

## REMARKS

Claims 14-26 are pending.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

### **I. Rejection of the Claims Over Sato et al. and/or Kishimoto et al. in view of Gross et al. and Farkas et al.**

The examiner rejects claims 14-26 under 35 U.S.C. §103(a) as allegedly being unpatentable over Sato *et al.* and/or Kishimoto *et al.* in view of Gross *et al.* and Farkas *et al.* Applicants respectfully traverse the rejection.

As noted previously, to establish a *prima facie* case of obviousness, an examiner has the burden of demonstrating that the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention and that they should do so with a reasonable expectation of success. Applicants respectfully assert that the examiner has failed to meet this burden.

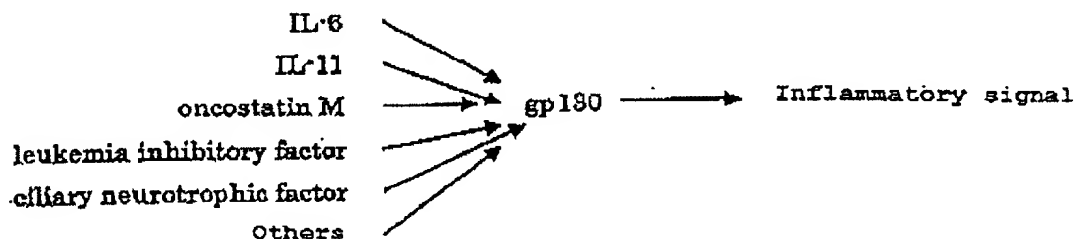
In particular, the examiner has failed to show that the prior art provided the requisite expectation of success. As shown in Mukaida *et al.* (previously submitted): (1) a cytokine, such as interleukin-6, exhibits various biological actions (Pleiotropy); (2) a plurality of cytokines exhibit the same action on the same cell (Redundancy); and (3) a plurality of cytokines are involved in the same cell line depending on the process of differentiation and growth. *See* English translation, pg. 5, ln. 5-17. In addition, Bellomo (previously submitted), taught that once a complicated network is activated, many cytokines belonging to the same network are produced.

Accordingly, at the time of the invention, an artisan would have expected that if an antagonist successfully blocked one cytokine, such as IL-6, another cytokine would likely compensate for the lost signal. Thus, for a given disease, such as pancreatitis, an artisan would not have reasonably expected that blocking a single cytokine would result in the prevention or amelioration of the disease. Indeed, the examiner voiced this same conclusion, noting that “the person of ordinary skill in the art would not expect that suppression of the

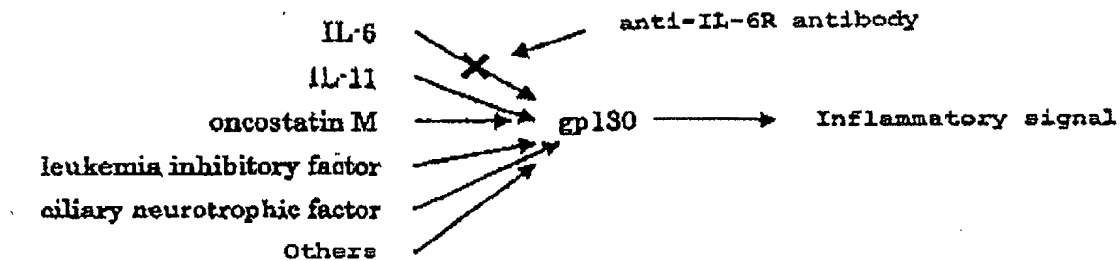
effects of a single cytokine would completely stop or prevent a condition that is due to the effects of multiple cytokines ...” Office Action dated October 6, 2003, pg. 3, ln. 6-10.

In fact, the cited art (especially Farkas) describes that in pancreatitis, levels of TNF and IL-6 increase, and that over-production of TNF and IL-6 play an important role in the pancreatic necrosis and development of extrapancreatic complication. However, considering the technical level in the art at the time the application was filed, one of ordinary skill in the art would not have expected that administering only an interleukin-6 antagonist would be effective for treating pancreatitis.

At the time of the invention, artisans understood the cytokine network to be quite complex. The IL-6 family of cytokines comprises a number of cytokines, such as IL-11, LIF, OSM, CNTF, CT-1, etc., with overlapping biological activities. *See* Taga, T. & Kishimoto, T., *Annu. Rev. Immunol.*, 15:797-819 (1997) at 799-801 (Enclosed). Taga *et al.* explained that the functional redundancy of the IL-6 family of cytokines arises from the nature of their receptor complexes, which all require gp130 for signal transduction. *Id.* at 801-802 and Figure 2. The referenced cytokine network can be described schematically as follows:



In light of this complexity and functional redundancy, an artisan at the time of the invention would have expected other cytokines to compensate for any blockage of IL-6 signal by an anti-IL-6 receptor antibody, as follows:



Accordingly, an artisan at the time of the invention would not have considered that inhibition of a single cytokine, IL-6, by an anti-IL-6 antagonist would be useful for treating pancreatitis, even if the relationship between IL-6 and pancreatitis were known.

In the present case, applicants surprisingly and unexpectedly discovered that administering an IL-6 antagonist can effectively prevent or ameliorate pancreatitis. This discovery was counter to the reasonable expectations of practitioners.

Applicant believes that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for

such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to  
Deposit Account No. 19-0741.

Respectfully submitted,

Date April 6, 2006

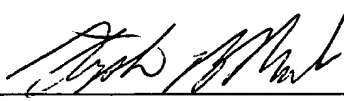
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